osteopenia had very low serum $24,25(OH)_2D$ concentrations and $24,25(OH)_2D$:25-OHD ratios.

Our data do not identify the site of the drugs' action. Anticonvulsants may affect $24,25(OH)_2D$ synthesis or catabolism directly. Alternatively, the primary effect of anticonvulsants may be to decrease gastrointestinal calcium absorption through end-organ hyporesponsiveness to $1,25(OH)_2D$,[13 14] leading to hypocalcaemia, secondary hyperparathyroidism,[5] raised serum $1,25(OH)_2D$ concentrations, and decreased serum $24,25(OH)_2D$ concentrations.

A reduction in the circulating concentrations of 25-OHD and possibly of other active metabolites of vitamin D is generally believed to play an important part in the pathogenesis of anticonvulsant-induced osteomalacia.[1-6 8] Recent studies have shown, however, that the serum concentration of $1,25(OH)_2D$ is normal or increased in patients on long-term treatment with anticonvulsant drugs.[8] The fact that the administration of vitamin D or 25-OHD corrects anticonvulsant-induced osteomalacia[9] raises the question whether another metabolite of vitamin D, essential for normal bone structure, is affected by anticonvulsants. Indeed, our findings suggest that $24,25(OH)_2D$ deficiency may be implicated in the pathogenesis of osteomalacia in patients receiving anticonvulsant drugs. This assumption is supported by recent observations[10 11] that $24,25(OH)_2D$ is important for normal ossification of bone.

Thus in patients in institutions and in northern populations in whom serum 25-OHD values are low the changes in 25-OHD metabolism may produce very low or undetectable concentrations of $24,25(OH)_2D$. On the other hand, the administration of vitamin D, which increases serum substrate (25-OHD) concentration, might enhance $24,25(OH)_2D$ synthesis and subsequently its serum concentrations despite the effect of the anticonvulsants.

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References

1 Richens, A, and Rowe, D J F, *British Medical Journal*, 1970, **4**, 73.
2 Dent, C E, *et al*, *British Medical Journal*, 1970, **4**, 69.
3 Hunter, J, *et al*, *British Medical Journal*, 1971, **4**, 202.
4 Hahn, T J, *et al*, *New England Journal of Medicine*, 1975, **292**, 550.
5 Bouillion, R, *et al*, *Journal of Clinical Endocrinology and Metabolism*, 1975, **41**, 1130.
6 Hahn, T J, *et al*, *Journal of Clinical Investigation*, 1972, **51**, 741.
7 Silver, J, Neale, G, and Thompson, G R, *Clinical Science and Molecular Medicine*, 1974, **46**, 433.
8 Jubiz, W, *et al*, *Journal of Clinical Endocrinology and Metabolism*, 1977, **44**, 617.
9 Stamp, T C B, *et al*, *British Medical Journal*, 1972, **4**, 9.
10 Ornoy, A, *et al*, *Nature*, 1978, **276**, 517.
11 Bordier, P, *et al*, *Journal of Clinical Endocrinology and Metabolism*, 1978, **46**, 284.
12 Weisman, Y, Reiter, E, and Root, A, *Journal of Pediatrics*, 1977, **91**, 904.
13 Koch, H U, *Epilepsia*, 1972, **13**, 509.
14 Villareale, M, *et al*, *Science*, 1974, **183**, 671.

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High-carbohydrate diets and insulin-dependent diabetics

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Summary and conclusions

A high-carbohydrate-(HC)-modified fat diet was compared with a standard low-carbohydrate (LC) diabetic diet in 11 insulin-dependent diabetics. Basal and preprandial plasma glucose concentrations were appreciably lower when the patients received the HC diet derived chiefly from readily available cereal and vegetable sources (mean (± SE of mean) basal concentrations 6·7±1·2 mmol/l (121±22 mg/100 ml) with the LC diet and 4·3±0·7 mmol/l (77±13 mg/100 ml) with the HC diet; mean preprandial concentrations 11·1±1·2 mmol/l (200±22 mg/100 ml) LC diet and 8·9±1·3 mmol/l (160±23 mg/100 ml) HC diet). Total and low-density lipoprotein cholesterol concentrations were lower when patients took the HC diet (mean 4·4±0·2 and 2·4±0·3 mmol/l (170±8 and 93±12 mg/100 ml) compared with 4·9±0·2 and 3·2±0·2 mmol/l (189±8 and 124±8 mg/100 ml) respectively), and the ratio of high-density lipoprotein cholesterol to total cholesterol tended to rise. The average percentage of glycosylated haemoglobin did not differ between the two diets.

Thus several measures of carbohydrate and lipid metabolism appear to be more satisfactory when patients receive a HC diet, which is an acceptable alternative to that still recommended to most insulin-requiring patients.

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Introduction

We have shown in maturity-onset diabetes that a high-carbohydrate (HC) diet composed of readily available cereal foods and tuberous vegetables resulted in lower fasting and preprandial blood glucose concentrations than a standard low-carbohydrate (LC) diet.[1] In the present investigation we carried out a similar comparison in a group of insulin-dependent diabetics.

Patients and methods

After obtaining informed consent we recruited 12 established insulin-dependent diabetics (six men and six women) into this outpatient study. The mean (±SE of mean) total insulin requirement was 51±8 U/day (range 21-92 units). Eleven patients were on a twice-daily insulin regimen, and only one received a single daily

injection. The patients' mean (±SE of mean) age was 40±5 years, duration of diabetes 18±3 years, and percentage ideal body weight 109±3·8% (Metropolitan Life Assurance Co tables).

The experimental design was identical with that described for patients with maturity-onset diabetes.[1] A diet that was high in carbohydrate (about 60% daily energy from carbohydrate, 25% from fat; the HC diet) and in which the ratio of polyunsaturated to other fatty acids in the diet was at least 1:1 was devised for each patient. In each case the diet was isoenergetic to the LC diet routinely recommended to our patients, in which 40% of total daily energy is derived from carbohydrate and the ratio of polyunsaturated to other fatty acids is about 1:3. The HC diet was calculated after a detailed dietary interview carried out at the time of recruitment. The HC foods used were all readily available and were based on cereal-containing foods and tuberous vegetables. Simple sugars were avoided in both diets. The meals were closely similar to those detailed in our earlier report.[1]

Patients were randomly allocated into one of two diet groups: the first continued taking their usual LC diet with reinforcement of the classic dietary advice and the second started taking the HC diet. After six weeks the patients were admitted for a 24-hour metabolic profile (as described previously[1]) starting at 1730, after which they were asked to follow the alternative diet. A second profile was carried out after a further six-week period. Meals and snacks during the profiles were isoenergetic between the two diets. Meals were taken at 0830, 1230, and 1800, and snacks at 2130 and 1530.

During the 24-hour profile heparin samples were collected half- to two-hourly and briefly kept at 4°C before the plasma was separated and frozen for subsequent assay of glucose (GOD-perid, Boehringer) and C-peptide[2] (antisera provided by Ms L Hedding). Fasting (taken at 0800) serum and EDTA plasma were collected for triglyceride[3] and cholesterol[4] estimations. Lipoprotein cholesterol subfractions were assayed after manganese heparin[5] and sodium lauryl sulphate[6] precipitation procedures.

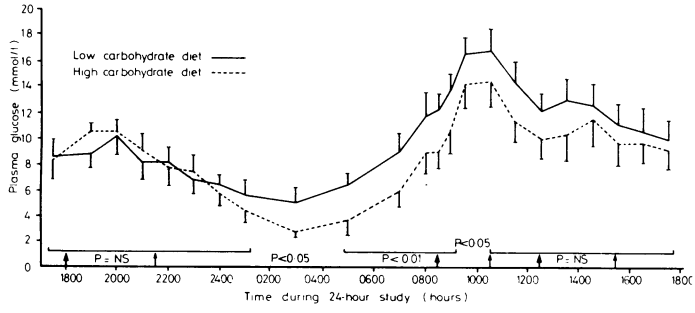
Dietary adherence was monitored by estimating the percentage change in the 18:2 fatty acid (linoleic acid) content of serum triglyceride,[1,7] and results are presented here for the 11 patients who appeared to be compliant using this method. Glycosylated haemoglobin was estimated on a fasting sample (taken at 0800) by cation exchange chromotography.[8] Plasma glucose control during the outpatient dietary periods was monitored weekly with home capillary-blood samples using the vacuum collector-bottle system.[9] As far as was possible in such an outpatient study the insulin dosage was altered to achieve comparable glucose concentrations with the two diets.

All results were expressed as means ±SE of mean. For statistical analysis we used Student's paired *t* test and the Wilcoxon matched-pairs test when the variables under consideration were not normally distributed.

Results

Plasma C-peptide concentrations—The mean C-peptide concentrations were extremely low throughout the day and similar with the two diets (table I).

Twenty-four-hour plasma glucose concentrations—The figure shows the 24-hour plasma glucose profile for both diets. With the HC diet the plasma glucose concentration was significantly lower between 0100 and 1030. Although the average 24-hour concentration remained lower through the remainder of the study, this did not reach significance. The mean basal plasma glucose concentration (average of values measure at 0300, 0500, and 0700) was significantly reduced on the HC diet, as was the mean preprandial plasma glucose concentration (average of values measured at 1730, 0830, and 1230; table I). The two 24-hour glucose profiles did not differ significantly in terms of either the area under the glucose curve or Schlichtkrull's "M" value[10] calculated from a baseline concentration of 4·5 mmol/l (81 mg/100 ml; table I).



Mean (±SE of mean) plasma glucose concentrations during 24-hour profiles while patients receiving low- and high-carbohydrate diets. Bold arrows indicate times of main meals; small arrows indicate times of snacks.
NS = Not significant.
Conversion: SI to traditional units—Plasma glucose: 1 mmol/l ≈ 18 mg/100 ml.

TABLE I—*Mean (±SE of mean) values for various measures of diabetic control and C-peptide concentrations with the two diets*

	Low-carbohydrate	High-carbohydrate	Significance*
Basal glucose (mmol/l)	6·7±1·2	4·3±0·7	P<0·01
Preprandial glucose (mmol/l)	11·1±1·2	8·9±1·3	P<0·05
Glucose area (mmol/l h)	9·1±1·0	8·3±0·7	NS
Schlichtkrull's "M" value	90·7±17·8	71·4±15·0	NS
Glycosylated haemoglobin (%)	11·0±0·7	11·1±0·6	NS
C-peptide (pmol/ml)	0·02±0·01	0·01±0·01	NS

*Significance of difference in "M" values calculated with Wilcoxon matched-pairs test; all other values calculated with Student's paired *t* test.
NS = Not significant.
Conversion: SI to traditional units—Glucose: 1 mmol ≈ 18 mg/100 ml.

Insulin—The average total daily insulin requirement was reduced with the HC diet from 51±8 U to 48±9 (P<0·01). This difference was principally accounted for by a reduction in the evening requirement (19±3 U LC diet and 15±3 U HC diet; P<0·02).

Glycosylated haemoglobin—The average percentage of glycosylated haemoglobin did not differ between the two diets (table I).

Weight—Although the prescribed diets were isoenergetic, most patients lost a small amount of weight with the HC diet. The average weight loss was 0·9±0·3 kg (P<0·02). There was no association, however, between the amounts of weight lost and the improvement in the basal plasma glucose concentration.

Serum triglycerides and plasma lipoprotein cholesterol concentrations—The fasting serum triglyceride concentrations did not differ between the two diets (table II). The total plasma cholesterol and low-density lipoprotein (LDL) cholesterol concentrations, however, both fell significantly with the HC diet (table II). Neither the high-density lipoprotein (HDL) nor the very-low-density lipoprotein cholesterol concentrations were affected by the change in diet, and consequently the ratio of HDL to total cholesterol rose from a mean of 33% with the LC diet to 37% with the HC diet.

TABLE II—*Mean (±SE of mean) total serum cholesterol and triglyceride and lipoprotein cholesterol concentrations with the two diets*

	Low-carbohydrate diet	High-carbohydrate diet	Significance*
Serum triglycerides (mmol/l)	1·20±0·13	1·09±0·08	NS
Total cholesterol (mmol/l)	4·9±0·2	4·4±0·2	P<0·001
HDL cholesterol (mmol/l)	1·6±0·1	1·6±0·1	NS
LDL cholesterol (mmol/l)	3·2±0·2	2·4±0·3	P<0·02
VLDL cholesterol (mmol/l)	0·2±0·1	0·5±0·2	NS

*Significance of difference in triglyceride concentrations calculated with Wilcoxon matched-pairs test; all other values calculated with Student's paired *t* test.
NS = Not significant. HDL = High-density lipoprotein. LDL = Low-density lipoprotein. VLDL = Very-low-density lipoprotein.
Conversion: SI to traditional units—Serum triglycerides: 1 mmol/l ≈ 89 mg/100 ml. Cholesterol: 1 mmol/l ≈ 39 mg/100 ml.

Discussion

The results of this study confirm that a diet high in carbohydrate does not cause diabetic control to deteriorate over several weeks. This is consistent with observations by other workers[11,12] in insulin-dependent diabetics and by ourselves[1,13] and others[14] in insulin-independent diabetics. Indeed, the substantial reduction in basal glucose concentration in the presence of a small reduction in evening insulin requirements

suggests that a HC diet will cause an improvement in diabetic control. This reduction in basal or fasting glucose with increased insulin sensitivity has been reported in non-diabetics[15] and insulin-requiring diabetics[12] receiving HC diets. Interestingly, Brunzell *et al*[12] achieved their results using an entirely digestible HC diet (Dextran) and observed a reduction in the fasting blood sugar concentration, while Miranda and Horwitz,[16] who altered only the non-digestible carbohydrate component of the diet, did not observe any effect on the fasting concentration. Thus, as with the maturity-onset diabetics, we believe that the main effect of the carbohydrate in our diet is attributable to the digestible component (cereal and tuberous starch) and that the extent to which the fibre contributes to the results cannot be stated.

Although the diets were isoenergetic, most patients lost a little weight on the HC diet. It became apparent that many of the patients had difficulty taking in the same amount of energy when transferred to the much bulkier HC diet, and this, we believe, explains the small weight reduction. The mean loss of weight, however, was less than 1 kg, and the absence of a positive relation between weight loss and improvement in control suggests that the improvement in basal glucose concentrations is not attributable to the weight loss.

In contrast with our findings in maturity-onset diabetics, we could not find any appreciable improvement in the percentage of glycosylated haemoglobin with the HC diet. One possible explanation for this is the problem of asymptomatic nocturnal hypoglycaemia, which many of our patients on twice-daily regimens have experienced. Over a period of time the morning hyperglycaemia occurring after the overnight hypoglycaemia may reverse any improvement in the percentage of glycosylated haemoglobin resulting from an improvement in overall diabetic control. Indeed, we might have obtained a more pronounced improvement in glucose control and possibly a reduction in glycosylated haemoglobin if we had been less conservative in reducing the insulin dosage during the HC diet. Once again the total cholesterol concentration fell, probably owing to fat modification and an increase in the ratio of polyunsaturated to other fatty acids in the diet. Furthermore, in insulin-requiring diabetics, unlike maturity-onset diabetics, dietary modification appears to reduce the LDL-cholesterol fraction while the HDL cholesterol remains unchanged, thus slightly increasing the ratio of HDL to total cholesterol.

We suggested[1] that a long-term prospective study would be required to evaluate whether the apparently more satisfactory metabolic control observed with the HC diet would benefit diabetics in the long term. In view of this considerable improvement in measures of carbohydrate and lipid metabolism observed in both insulin-requiring and maturity-onset patients, however, such a trial may perhaps never be carried out.

We are grateful to the patients who gave up their time to participate in this study. We also acknowledge the advice and encouragement of Drs R C Turner and R A Moore; the help of Mrs M Beeton, Mrs E Harris, Mrs C Uren, Mrs S Humphreys, Mrs C Whittle, and Dr J Land; and the help of Mrs A Reeve and Mrs B Carter in preparing the manuscript.

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References

1 Simpson, R W, *et al*, *British Medical Journal*, 1979, **1**, 1753.
2 Hedding, L, Novo Research Institute. Personal communication, 1976.
3 Eggstein, K, and Kreutz, F H, *Klinische Wochenschrift*, 1966, **44**, 262.
4 Huang, T C, *et al*, *Analytical Chemistry*, 1961, **33**, 1405.
5 Burstein, M, Scolnick, H R, and Morfin, R, *Journal of Lipid Research*, 1970, **11**, 583.
6 Onongba, I C, and Lewis, B, *Clinica Chimica Acta*, 1976, **71**, 397.
7 Moore, R A, *et al*, *Clinical Endocrinology*, 1977, **7**, 143.
8 Kynoch, P A M, and Lehmann, H, *Lancet*, 1977, **2**, 16.
9 Howe-Davies, S, *et al*, *British Medical Journal*, 1978, **2**, 596.
10 Schlichtkrull, J, Munck, O, and Jessild, M, *Acta Medica Scandinavica*, 1965, **177**, 95.
11 Weinsier, R L, *et al*, *Annals of Internal Medicine*, 1974, **30**, 332.
12 Brunzell, J D, *et al*, *Diabetes*, 1974, **23**, 138.
13 Hockaday, T D R, *et al*, *British Journal of Nutrition*, 1978, **39**, 357.
14 Kiehm, T G, Anderson, J W, and Ward, K, *American Journal of Clinical Nutrition*, 1971, **285**, 1450.
15 Himsworth, H P, *Clinical Science*, 1933, **1**, 3.
16 Miranda, P M, and Horwitz, D L, *Annals of Internal Medicine*, 1978, **88**, 482.

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ONE HUNDRED YEARS AGO The admirable paper of Dr Cornelius Fox, read before the last meeting of the British Medical Association and published in the BRITISH MEDICAL JOURNAL of December 7th, places before the profession in a clear light the symptoms of a throat-affection, which he most aptly terms "spreading quinsy."

Early last spring, I attended a large number of patients suffering from this complaint. In a district a few miles off, there was a pretty severe epidemic of diphtheria at the same time, and consequently there was much anxiety lest we should have an outbreak of this most dangerous disease. I carefully examined each case that came under my notice, and I was convinced that not one of them could be considered to be true diphtheria; and, being at a loss for a term to describe the affection, I named it in my note-book "epidemic quinsy." In each case, I found that there was some sanitary defect in the residence or in the immediate neighbourhood of the patient, proving conclusively to my mind that this belongs to that class of disorders termed filth-diseases.

At the commencement, the patient complains of lassitude, pains in the limbs, slight shiverings, and disordered stomach. Some marked pyrexia sets in, and, at the same time, pricking sensations in the throat, with an attendant propensity to constant hawking, are complained of. On examination of the throat, the tonsils are seen to be enlarged and inflamed, the redness extending over the pharynx and fauces, and involving the uvula. Yellowish opaque spots, and sometimes even large patches, subsequently appear on the tonsils. These can be easily detached, and probably consist only of the accumulated secretions from the follicles. There is much tenderness under the jaw, and the salivary and adjacent lymphatic glands are generally swollen and painful. I have observed that, in these cases, the tonsils do not become enlarged to anything like the extent usually met with in a severe attack of ordinary cynanche tonsillaris, and that they are of a deeper and more livid hue, and a more glazed and shining appearance. The pulse soon exceeds 100, and the temperature generally rises to about 102 deg; in one case, it reached as high as 10·38 deg. Towards evening, there is occasionally slight delirium, and almost invariably great restlessness. The urine in no case contains any trace of albumen; it is distinctly febrile, and there is a marked deficiency of the chlorides. The patient soon becomes very weak and low, and the difficulty in swallowing tends still further to increase the prostration. The case is generally at the worst on the fifth or sixth day, after which the patient gradually commences to improve; there is no crisis, and, as a rule, the tonsils do not suppurate. I have never noticed sequelae of any kind, with the exception perhaps of slight weakness of the throat, and an increased tendency to take cold.

As to treatment, I found it best, at the outset of the case, to administer a saline aperient, and then, for the first two or three days, to give a saline mixture. Subsequently, tonics, and especially quinine, are not only serviceable, but in most cases even necessary. When the patient becomes feverish, restless, and feeble, I have found a moderate quantity of wine decidedly beneficial. Milk and beef-tea form the best food throughout, as they are comparatively easy to swallow, and, of course, highly nutritious. A warm atmosphere is the best, and frequent irrigation of the throat with warm water is productive of considerable benefit. Where the patches have been unusually adherent, and the inflammation more than ordinarily severe, I have painted the tonsils with tincture of steel and glycerine. Within a fortnight, the patient is almost invariably convalescent. (*British Medical Journal*, 1879.)